

## CLINICAL PRACTICE

# Stimulation induced variability of pulse plethysmography does not discriminate responsiveness to intubation

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**Background.** Hypnotic depth but not haemodynamic response to painful stimulation can be measured with various EEG-based anaesthesia monitors. We evaluated the variation of pulse plethysmography amplitude induced by an electrical tetanic stimulus (PPG variation) as a potential measure for analgesia and predictor of haemodynamic responsiveness during general anaesthesia.

**Methods.** Ninety-five patients, ASA I or II, were randomly assigned to five groups [Group 1: bispectral index (BIS) (range) 40–50, effect site remifentanyl concentration 1 ng ml<sup>-1</sup>; Group 2: BIS 40–50, remifentanyl 2 ng ml<sup>-1</sup>; Group 3: BIS 40–50, remifentanyl 4 ng ml<sup>-1</sup>; Group 4: BIS 25–35, remifentanyl 2 ng ml<sup>-1</sup>; Group 5: BIS 55–65, remifentanyl 2 ng ml<sup>-1</sup>]. A 60 mA tetanic stimulus was applied for 5 s on the ulnar nerve. From the digitized pulse oximeter wave recorded on a laptop computer, linear and non-linear parameters of PPG variation during the 60 s period after stimulation were computed. The haemodynamic response to subsequent orotracheal intubation was recorded. The PPG variation was compared between groups and between responders and non-responders to intubation (ANOVA). Variables independently predicting the response were determined by logistic regression.

**Results.** The probability of a response to tracheal intubation was 0.77, 0.47, 0.05, 0.18 and 0.52 in Groups 1–5, respectively ( $P < 0.03$ ). The PPG variability was significantly higher in responders than in non-responders but it did not improve the prediction of the response to tracheal intubation based on BIS level and effect site remifentanyl concentration.

**Conclusion.** Tetanic stimulation induced PPG variation does not reflect the analgesic state in a wide clinical range of surgical anaesthesia.

*Br J Anaesth* 2006; **96**: 323–9

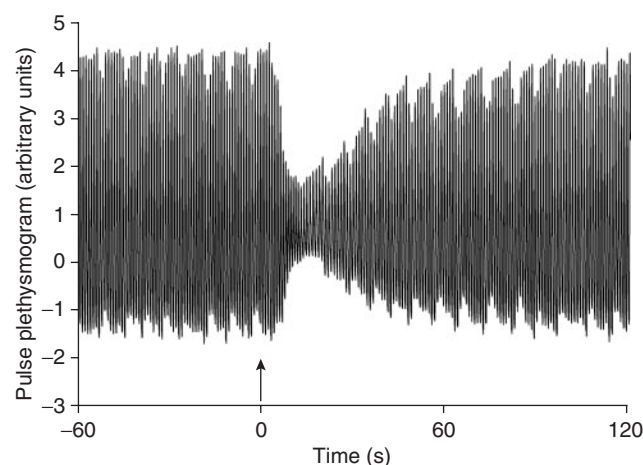
**Keywords:** anaesthesia, depth; measurement techniques, pulse plethysmography; monitoring, bispectral index

Accepted for publication: December 8, 2005

While several types of hypnotic state monitors are commercially available,<sup>1,2</sup> no monitor can measure adequacy of analgesia or predict haemodynamic response to painful stimulation during general anaesthesia. The EEG-based hypnotic state monitors do not provide parameters predictive of haemodynamic reaction or movement,<sup>3</sup> although the EEG response to noxious stimulation may reflect the analgesic drug concentration.<sup>4</sup> Analgesic drugs are therefore administered according to the response of the patient to surgical stimulation. Remifentanyl dose-dependently blocks the haemodynamic response to tracheal intubation.<sup>4</sup> The bispectral index (BIS) level was shown to independently correlate with the haemodynamic response to tracheal

intubation in an early trial<sup>5</sup> but not in subsequent studies.<sup>6,7</sup> Anaesthetic drug concentrations, although inversely correlated with the probability of a haemodynamic response, do not allow a reliable prediction in the individual subject because of the variation in anaesthetic drug requirement. A method for measuring the analgesic state in an anaesthetized patient might help to assess the inter-individual variation of pharmacodynamic drug effect and enable the anaesthesiologist to avoid unexpected haemodynamic reactions to strong stimuli without overdosing analgesic drugs.

A short electrical stimulation of the ulnar nerve elicits a short vasoconstriction measurable with pulse plethysmography (PPG) (Fig. 1), which is suppressed by increasing



**Fig. 1** PPG curve of a typical subject from 60 s before and 120 s after electrical stimulation of the ulnar nerve (arrow).

plasma concentrations of alfentanil.<sup>8</sup> Suppression of this short vasoconstriction has been associated with the absence of a relevant haemodynamic response to subsequent tracheal intubation.<sup>8</sup> The purpose of this study was to confirm these preliminary results and to further explore the PPG response to painful stimulation.

In the present randomized, controlled and double-blinded study, the stimulation-induced variation of PPG was determined in patients at different levels of surgical anaesthesia. BIS level, remifentanyl concentration and the parameters derived from PPG were correlated with haemodynamic response to tracheal intubation. We hypothesized that PPG parameters would discriminate the different levels of anaesthesia, which were defined by different BIS levels and different effect site remifentanyl concentrations, and would offer the potential to quantify haemodynamic responsiveness and analgesia in anaesthetized patients.

## Materials and methods

After approval by the local Ethics Committee and obtaining written informed consent, 95 patients (ASA I or II) undergoing elective surgery under general anaesthesia were enrolled. Patients with cardiovascular disease (hypertension or antihypertensive treatment, cardiac, cerebrovascular or peripheral vascular disease), relevant pulmonary, liver, kidney or central nervous system disease, diabetes mellitus, alcohol or drug abuse, and patients with a difficult airway (Mallampati class 3 or higher) or unable to give informed consent were excluded.

After a fasting period of 6 h and premedication with midazolam 7.5 mg given orally 30 min before induction, the patients were monitored using ECG, non-invasive blood pressure cuff and pulse oximeter (Datex AS3 monitor; Datex-Ohmeda, Instrumentarium Corporation, Helsinki, Finland), with the pulse oximeter probe placed on the third finger of the non-dominant arm. A venous cannula was inserted on the ipsilateral forearm and an infusion of Ringer's lactate was started with a flow rate of 2 ml kg<sup>-1</sup> h<sup>-1</sup>.

**Table 1** Treatment groups

	Target BIS (range)	Remifentanyl bolus (µg kg <sup>-1</sup> )	Remifentanyl infusion rate (µg kg <sup>-1</sup> min <sup>-1</sup> )
Group 1	40–50	0.2	0.04
Group 2	40–50	0.4	0.08
Group 3	40–50	0.8	0.20
Group 4	25–35	0.4	0.08
Group 5	55–65	0.4	0.08

The blood pressure cuff was attached on the opposite arm. An A2000 XP-BIS monitor (BIS software version 3.3; Aspect Medical Systems, Natick, MA, USA) was installed with the sensor placed frontally according to the manufacturer's guidelines.

Skin electrodes for electrical stimulation of the ulnar nerve were placed along a line between point A (1 cm ulnar to the mid-point of the cubital fold) and point B (1.5 cm ulnar to the mid-point of the first wrist fold) on the dominant arm 15 and 23 cm distal to A.<sup>9</sup> They were connected to a Digitimer DS 7 constant current stimulator with a Digitimer DG2 trigger generator (Digitimer Ltd, Hertfordshire, UK) and a timer device (constructed in our laboratory) with the positive pole attached proximally.

Before induction of anaesthesia the patients were randomly assigned to five treatment groups (Table 1) differing in BIS level and remifentanyl infusion rate, using a stratified randomization protocol.<sup>10</sup> After a simulation using the pharmacokinetic and pharmacodynamic parameters set by Minto and colleagues,<sup>11</sup> the remifentanyl boluses and infusion rates were chosen in order to achieve predicted effect site remifentanyl concentrations of 1, 2 or 4 ng ml<sup>-1</sup>. The different BIS levels were achieved by propofol target plasma concentrations between 2.2 and 4.0 µg ml<sup>-1</sup>.

For induction of anaesthesia the selected bolus of remifentanyl was given i.v., followed by the related continuous infusion of remifentanyl. A target-controlled infusion of propofol was started with the propofol plasma target concentration adjusted to achieve and maintain the selected BIS level. Muscle relaxation was achieved with i.v. vecuronium 0.15 mg kg<sup>-1</sup> given after loss of consciousness. After achieving the maximal effect of vecuronium, verified by train-of-four (suppression of at least three of four twitches), a 5 s, 60 mA, 50 Hz, 0.25 ms square-wave electrical stimulus<sup>12</sup> was applied to the ulnar nerve. After blood pressure and HR had returned to the pre-stimulation level, an experienced anaesthetist, blinded to the allocation of the patient to a particular group, performed tracheal intubation. During the study the arterial pressure was measured non-invasively (oscillometric method) at 1 min intervals. The study ended 5 min after tracheal intubation. During the study no vasoactive drugs were given. In case of hypotension (mean arterial pressure <60 mm Hg) a rapid infusion of Ringer's lactate 250–500 ml was given and the patient was put into head-down position.

The room temperature was 20°C and the patients were covered with a warming blanket (Bair Hugger®; Arizant Inc., MN, USA).

Blood pressure, HR, end-tidal carbon dioxide and  $Sp_{O_2}$  were recorded on a laptop computer every 10 s. The BIS values from the A2000 monitor were recorded every 5 s. The quality of visualization of the vocal cords (Wilson and colleagues<sup>13</sup>) and the duration of intubation were recorded. Patients with prolonged intubation time (>45 s) were excluded from the study. The infusion rate of remifentanyl was also recorded on a laptop computer every 10 s.

The PPG signal was digitized at 128 Hz (A/D conversion card; National Instruments Corporation, Austin, TX, USA) for off-line analysis.

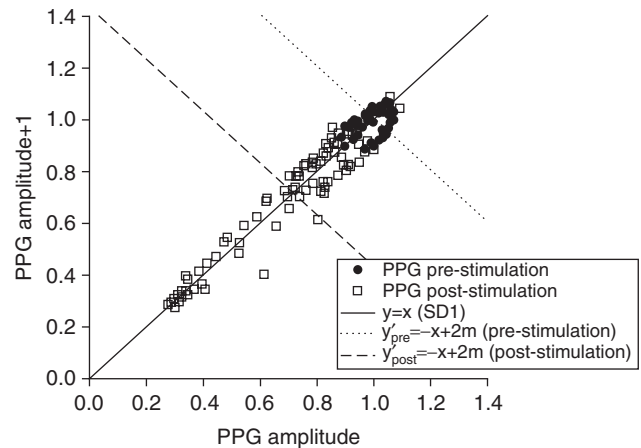
HR, systolic and diastolic blood pressure, and BIS were extracted from the files and the mean (SD) values were calculated for the 120 s periods before induction of anaesthesia, before electrical stimulation (after induction of anaesthesia) and before laryngoscopy. The maximal HR, blood pressure and BIS in the 300 s after tracheal intubation were determined. An increase in systolic arterial pressure of >20 mm Hg and/or maximal HR after intubation more than 90 were defined as a response to tracheal intubation.<sup>14</sup>

The recorded signals from the periods before (60 s before tetanic stimulus) and after the stimulus (60 s after the onset of tetanic stimulus) were analysed off-line. The PPG parameters for these periods were computed as described below.

For each heartbeat, PPG amplitude and relative horizontal PPG notch position were measured and the corresponding beat-to-beat time series were constructed. The amplitude of the PPG and the location of the PPG dicrotic notch were detected automatically. Subsequently, these automatic detections were verified visually and corrected in case of misdetection. All heartbeats with PPG artifacts or movement artifacts were excluded from the analysis. Pulse waveforms where the dicrotic notch could not be identified were also excluded.

The stimulation-induced variability of the PPG amplitude was measured by the minimal PPG amplitude after stimulation, normalized to the value before stimulation. In a second analysis more sophisticated parameters were computed: the ratio of the standard deviation (SD ratio) of PPG amplitude after/before stimulus, the relative notch position after/before stimulus and SD1 and SD2 determined with Poincaré analysis (P-SD1, P-SD2, see below).

The quantitative Poincaré analysis was carried out as suggested by Tulppo and colleagues.<sup>15</sup> In this analysis, PPG is plotted (Fig. 2) on an  $x$ - $y$  plane so that the current PPG amplitude (on the  $y$ -axis) is related to the previous PPG amplitude (on the  $x$ -axis). The Poincaré analysis provides a qualitative way of detecting deterministic patterns in complex data. For quantitative analysis of the plot the SDs of the Poincaré plot against the axes  $y=x$  (P-SD1) and  $y'=-x+2m$  (P-SD2), where  $m$  is the mean PPG during the epoch of interest, and their ratio (P-SD1/P-SD2) were



**Fig. 2** Poincaré plot of the response to tetanic stimulation. Data points before and after stimulation (closed circles and open squares, respectively). Solid line  $y=x$ , dotted line  $y'_{pre}=-x+2m$ , with  $m$ =mean of PPG pre-stimulation, dashed line  $y'_{post}=-x+2m$ , with  $m$  = mean of PPG post-stimulation.

calculated. P-SD1 describes mainly fast beat-to-beat PPG variability, while P-SD2 describes slower components of PPG variability.<sup>15</sup> The stimulation-induced variability of the PPG would therefore be represented by an increase of P-SD2.

### Statistical analysis

Patients were stratified according to gender and age (<30, 30–55 and >55 yr) and randomized to the five groups using the minimization method.<sup>10</sup> If the number of subjects of a given gender and age group previously allocated to the groups was similar, allocation was performed with a random number table generated with Excel (Microsoft Office 2000). With the selected treatment protocols we aimed to achieve an important number of responders and non-responders in the study population with significant differences of the responder vs non-responder ratio between groups.

The PPG values after the tetanic stimulus were normalized with respect to their pre-stimulus values by dividing the post-stimulus values by their pre-stimulus values. The normalized data of all five treatment groups were compared, as were the data of the three groups with similar remifentanyl and similar BIS levels, using ANOVA on ranks.  $P<0.05$  was considered statistically significant. SPSS for Windows® v11.01 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses.

The patients were then classified as responders or non-responders according to their haemodynamic response to tracheal intubation. The proportions of responders to intubation in the five groups were compared with a  $\chi^2$ -test. The pre-intubation BIS level, the calculated effect site remifentanyl concentration, and the different PPG variables were compared between responders and

non-responders using signed rank test,  $P < 0.05$  considered significant. The different PPG variables were entered in a logistic regression analysis to determine their predictive value with respect to the responder status. The performance of the resulting equation predicting the responder status was assessed by leave-one-out cross-validation. The predicted responder status was computed for each subject according to the logistic regression equation. The performance of the test was further evaluated by receiver operator characteristic (ROC) analysis.

## Results

Ninety-five patients (57 women and 38 men) were enrolled. Four subjects were excluded from data evaluation because of prolonged intubation ( $>45$  s); four additional subjects were excluded because the dicrotic notch could not be identified in the PPG signal; and one subject was excluded because of serious arrhythmia. The remaining 86 patients were included in the data analysis. The characteristics of the five treatment groups were similar (Table 2). The study was performed between 7:30 a.m. and 3:30 p.m.

The computed effect site remifentanyl concentrations, the BIS levels before tracheal intubation and the target plasma propofol concentrations, and the systolic arterial

pressure and HR increase induced by tracheal intubation, are given in Table 3. In the three groups with similar BIS and propofol and varying remifentanyl concentrations the systolic arterial pressure increase after tracheal intubation was significantly higher in Group 1 (lowest remifentanyl concentration) compared with Groups 2 and 3 and the HR increase was significantly lower in Group 3 (highest remifentanyl concentration) than in Groups 1 and 2. In the groups with similar remifentanyl concentration and varying BIS and propofol the systolic arterial pressure increase was significantly higher in Group 5 (highest BIS level) compared with Groups 2 and 4, whereas the HR increase was significantly lower in Group 4 (lowest BIS level) compared with Groups 2 and 5.

The incidence of a response to tracheal intubation (SAP increase  $>20$  mm Hg or maximal HR  $>90$  min<sup>-1</sup>) was significantly different between all groups ( $P < 0.03$ , Table 3).

The stimulation-induced PPG variability was similar between treatment groups (Table 4).

Of the 86 patients included in the analysis, 33 were responders and 53 were non-responders. Of all the parameters, only the predicted effect site remifentanyl concentration before intubation, the BIS level before intubation and the PPG variation induced by tetanic stimulation as reflected by the P-SD2 were significantly different between

**Table 2** Characteristics of the study population. The data are mean (SD) or numbers of patients. Groups were compared with one-way ANOVA and  $\chi^2$  as appropriate. SAP, systolic arterial pressure; DAP, diastolic arterial pressure; HR, heart rate (all values on the ward the day before surgery). \*Paired *t*-test:  $P < 0.001$  compared with tympanic temperature before induction of anaesthesia

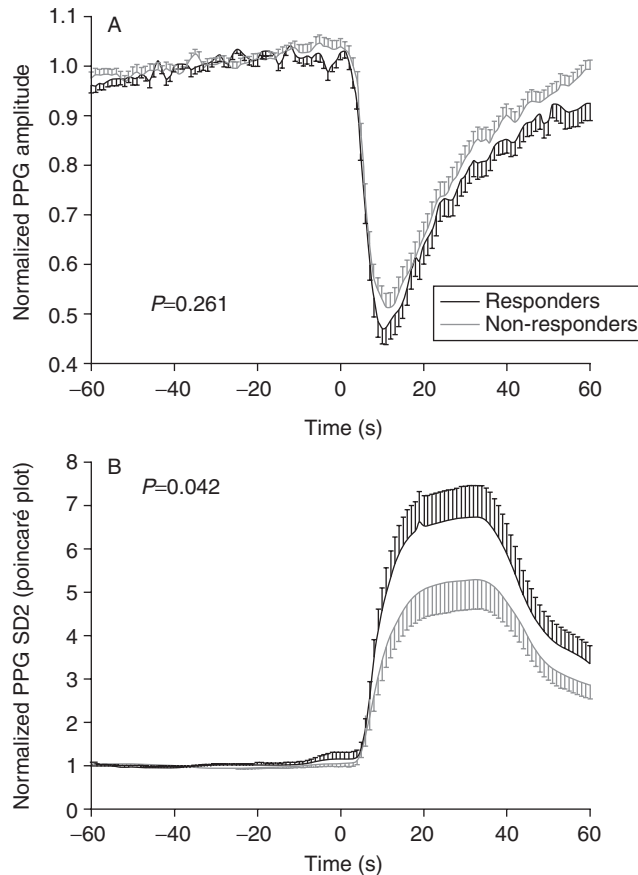
	Group 1	Group 2	Group 3	Group 4	Group 5	<i>P</i> -values
Age (yr)	39.5 (22–56)	40 (22–59)	39.1 (19–59)	36.1 (23–58)	40.5 (19–60)	0.723
Gender (m/f)	7/5	7/12	7/12	7/10	8/11	0.885
Weight (kg)	72.2 (12.7)	68.2 (11.3)	69.3 (13.2)	69.1 (14.9)	74.9 (17.1)	0.593
BMI (kg m <sup>-2</sup> )	24.8 (2.8)	23.9 (3.7)	23.8 (3.2)	22.9 (3.1)	25.4 (4.2)	0.248
ASA I/II	10/3	14/5	16/3	13/4	16/3	0.902
SAP (mm Hg)	120 (9)	118 (12)	118 (14)	122 (12)	120 (12)	0.889
DAP (mm Hg)	79 (8)	74 (8)	75 (9)	74 (8)	76 (10)	0.661
HR (beats min <sup>-1</sup> )	72 (10)	75 (6)	75 (8)	74 (12)	73 (10)	0.904
Laryngoscopy (Wilson and colleagues <sup>13</sup> I/II/III)	11/2/0	15/4/0	12/6/1	14/3/0	13/5/1	0.795
Duration of intubation (s)	18.5 (11.0)	16.3 (4.9)	16.9 (4.4)	16.4 (4.9)	17.2 (3.7)	0.840
Skin temperature at stimulation (°C)	33.0 (2.2)	34.0 (1.8)	34.0 (1.4)	34.0 (1.3)	33.2 (1.4)	0.091
Tympanic temperature before induction (°C)	37.3 (0.3)	37.2 (0.4)	37.2 (0.6)	37.3 (0.3)	37.1 (0.5)	0.583
Tympanic temperature after induction (°C)	36.8 (0.25)*	36.7 (0.5)*	36.7 (0.5)*	36.9 (0.4)*	36.7 (0.5)*	0.291

**Table 3** BIS level, anaesthetic drug concentrations and response to tracheal intubation in the five treatment groups. Values are mean (SEM). BIS, BIS level before tracheal intubation; Remifentanyl, predicted effect site remifentanyl concentration (ng ml<sup>-1</sup>); Propofol, predicted plasma propofol concentration (µg ml<sup>-1</sup>); SAP increase, increase in systolic arterial pressure after tracheal intubation compared with the mean systolic arterial pressure during 2 min before intubation; HR max, maximal heart rate after tracheal intubation; *P* response, probability of response to tracheal intubation. ANOVA on ranks: \* $P < 0.05$  compared with the other treatment groups; \*\* $P < 0.05$  compared with Group 5; † $P < 0.05$  compared with Groups 3 and 5; ‡ $P < 0.05$  compared with Groups 3 and 4; § $P < 0.05$  compared with Groups 1 and 2

	Group 1	Group 2	Group 3	Group 4	Group 5	<i>P</i> -values
<i>N</i>	12	19	19	17	19	
BIS	46 (1.4)	45 (1.5)	43 (1.2)	32 (1.0)*	57 (0.9)*	$<0.001$
Remifentanyl	1.1 (0.02)*	2.1 (0.07)*	4.7 (0.17)*	2.0 (0.05)	2.1 (0.07)	$<0.001$
Propofol	3.4 (0.9)**	3.2 (0.9)**	2.9 (0.7)	4.0 (0.8)†	2.2 (0.5)	$<0.001$
SAP increase (mm Hg)	29 (4.7)‡	16 (2.4)	11 (2.5)**	12 (1.8)	24 (3.4)	$<0.001$
HR max (min <sup>-1</sup> )	84 (3.6)	85 (2.7)	67 (2.5)‡	73 (2.5)	76 (2.6)	$<0.001$
<i>P</i> response	0.77	0.47	0.05	0.18	0.52	0.03

**Table 4** PPG responses to electrical stimulation of the ulnar nerve in the five treatment groups. Values are mean (SEM). PPG responses to electrical stimulation are normalized to the values before stimulation: value after stimulation divided by value before stimulation. Min. PPG amplitude, minimal PPG amplitude after stimulation; SD ratio, ratio of SD of the mean PPG amplitude before/after stimulus; Relative notch position, notch amplitude divided by total PPG amplitude; Mean PPG amplitude, mean PPG amplitude after stimulation; P-SD1 and P-SD2, SD of the residuals of the PPG amplitude to the Poincaré lines  $y=x$  and  $y=-x+2m$ , respectively. ANOVA on ranks: significance level  $P<0.05$

	Group 1	Group 2	Group 3	Group 4	Group 5	P-values G1-2-3	P-values G2-4-5	P-values all
Min. PPG amplitude	0.454 (0.063)	0.429 (0.040)	0.485 (0.045)	0.442 (0.040)	0.436 (0.039)	0.748	0.934	0.916
SD ratio (PPG amplitude)	3.49 (0.58)	4.56 (0.75)	2.97 (0.48)	3.02 (0.37)	3.30 (0.45)	0.239	0.409	0.509
Relative notch position	0.984 (0.013)	0.964 (0.098)	0.972 (0.008)	1.002 (0.044)	0.982 (0.011)	0.802	0.599	0.860
Mean PPG amplitude	0.775 (0.033)	0.807 (0.025)	0.826 (0.025)	0.818 (0.025)	0.759 (0.040)	0.435	0.366	0.461
P-SD1	1.59 (0.26)	1.46 (0.12)	1.23 (0.09)	1.26 (0.09)	1.39 (0.13)	0.324	0.241	0.466
P-SD2	3.98 (0.67)	5.10 (0.89)	3.28 (0.55)	3.30 (0.43)	3.53 (0.48)	0.201	0.454	0.487
P-SD1/P-SD2	0.52 (0.12)	0.42 (0.06)	0.50 (0.06)	0.46 (0.05)	0.48 (0.06)	0.483	0.429	0.726



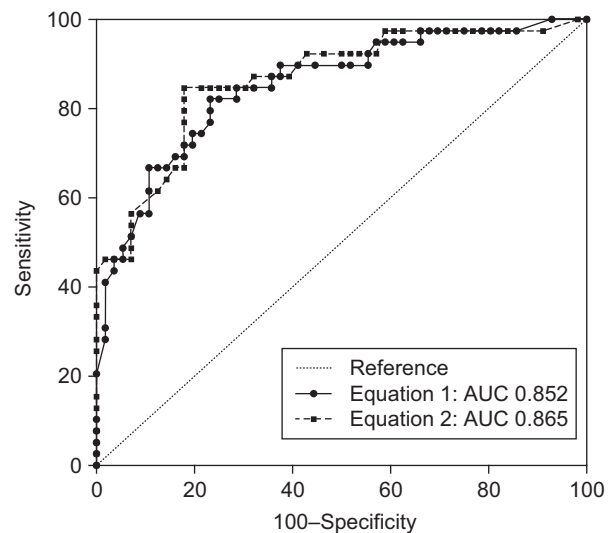
**Fig. 3** PPG amplitude (A) and Poincaré SD2 (B). Averaged curves of responders (black) and non-responders (grey) to tetanic stimulus. P-SD2 has been computed over a sliding window of 30 previous heartbeats.

responders and non-responders (Fig. 3 and Table 5). The responses as quantified by the other PPG parameters were not statistically different. In the multivariate logistic regression the predicted remifentanyl effect site concentration and the BIS level before intubation were the strongest predictors of the response to tracheal intubation [equation (1)].

$$P_{\text{response}} = \frac{1}{1 + e^{-(0.058 \times \text{BIS}_{\text{preintub}} - 1.131 \times \text{Remifentanyl}_{\text{preintub}} - 0.512)}} \quad (1)$$

**Table 5** BIS level, anaesthetic drug concentrations before tracheal intubation and PPG variation after electrical stimulation in responders and non-responders to tracheal intubation. Min. PPG amplitude, minimal PPG amplitude after stimulation; SD ratio, ratio of SD of the mean PPG amplitude before/after stimulus. Relative notch position, notch amplitude divided by total PPG amplitude; Mean PPG amplitude, mean PPG amplitude after stimulation; P-SD1 and P-SD2, SD of the residuals of the PPG amplitude to the Poincaré lines  $y=x$  and  $y=-x+2m$ , respectively. Signed rank test: significance level  $P<0.05$

	Responders	Non-responders	P-values
BIS pre-intubation	46.4 (1.9)	41.0 (1.3)	0.015
Effect site remifentanyl (ng·ml <sup>-1</sup> )	1.83 (0.13)	2.89 (0.19)	<0.001
Propofol pre-intubation	3.1 (1.0)	3.2 (0.9)	0.94
Min. PPG amplitude	0.430 (0.029)	0.461 (0.026)	0.507
Relative notch position	0.974 (0.008)	0.984 (0.015)	0.686
SD ratio (PPG amplitude)	3.99 (0.42)	3.16 (0.30)	0.062
Mean PPG amplitude	0.813 (0.017)	0.776 (0.023)	0.178
P-SD1	1.51 (0.12)	1.29 (0.06)	0.176
P-SD2	4.51 (0.49)	3.42 (0.34)	0.042
P-SD1/SD2	0.442 (0.052)	0.492 (0.034)	0.093



**Fig. 4** ROC curves of the probability of a response to tracheal intubation computed according to equations (1) and (2) (see text), respectively. The predicted effect site remifentanyl concentration and the BIS level were variables in equation (1), the same variables and the SD ratio of the tetanic stimulation-induced PPG variation in equation (2) (for further details see text). The area under the curve (AUC) of ROC 1 and ROC 2 are similar ( $P=0.543$ ).



The SD ratio (PPG amplitude) was the only other significant parameter predicting the response to tracheal intubation [equation (2)].

$$P_{\text{response}} = \frac{1}{1 + e^{-[0.060 \times \text{BISpreintub} - 1.149 \times \text{Remifentanilpreintub} + 0.157(\text{PPGSDpost}/\text{PPGSDpre}) - 1.111]}} \quad (2)$$

The probability of response according to equations (1) and (2) was computed for each subject. ROC curves were computed with the calculated response probabilities without and with inclusion of PPG variation (Fig. 4). With a probability of response=0.5 as cut-off value the sensitivity and specificity of the predictions were 72 and 80% [equation (1)] and 80 and 82% [equation (2)], respectively. The area under the ROC curves of the two predictions was similar (Fig. 4).

## Discussion

With BIS levels between 30 and 60, predicted propofol plasma concentrations between 2 and 4  $\mu\text{g ml}^{-1}$ , predicted remifentanil effect site concentrations between 1.1 and 4.7  $\text{ng ml}^{-1}$  and a probability of haemodynamic response to tracheal intubation between 5 and 75%, our five study groups represent clinically relevant levels of surgical anaesthesia. In this setting, the investigated parameters of stimulation-induced PPG variability poorly reflected different levels of drug concentrations and hence surgical anaesthesia, and did not improve the prediction of haemodynamic response to tracheal intubation.

Although the selected tetanic stimulation did not induce a relevant haemodynamic response, the PPG response was considerable and was dose-dependently suppressed in the previous trial (plasma concentrations up to 220  $\text{ng ml}^{-1}$ ).<sup>8</sup> According to the EEG effect 220  $\text{ng ml}^{-1}$  of alfentanil are equipotent as 4.4  $\text{ng ml}^{-1}$  of remifentanil.<sup>16</sup> A well-defined and repeatable non-noxious pain stimulus with a sensitive response measure was therefore considered an ideal set-up to quantify haemodynamic responsiveness and analgesia. In the previous trials on PPG<sup>8</sup> or laser-Doppler skin vasomotor reflex<sup>9</sup> a tetanic stimulus was applied at incrementing concentrations of an alfentanil or sevoflurane until the response signal was suppressed. A suppressed response signal then predicted suppression of the response to subsequent tracheal intubation. In the current study the stimulation-induced PPG variability was determined only once at a given drug concentration. In our previous study vasoconstriction was expressed as the maximal change of the PPG amplitude in per cent of the value before stimulation,<sup>8</sup> and the stimulation-induced PPG deflection was considered suppressed if the maximal deflection of the PPG amplitude after stimulation was <10% of the value before stimulation.<sup>8</sup>

In the current study the maximal PPG deflection was >10% of the value before stimulation in most patients

(data not shown). We therefore analysed additional parameters such as the SD ratio of the PPG and the Poincaré SD2 reflecting not only the maximal deflection but also the time course of the PPG variation. Because the stimulation-induced vasoconstriction implies a non-stationary signal we considered the non-linear analysis based on the Poincaré plot<sup>15</sup> more appropriate than the linear time domain parameters. The Poincaré SD1 and SD2 are more robust parameters than the maximal post-stimulation deflection of a variable and are less affected by possible outliers or artifacts. Especially P-SD2 is not only affected by the maximal deflection but also by the rate of recovery and eventually by the amount of other variations in the signal, which may potentially reflect some autonomic control mechanisms. However, even P-SD1 and P-SD2 did not discriminate between the five treatment groups. The P-SD2 response, but not the minimal PPG amplitude after stimulation, was significantly different in responders than in non-responders. The difference of PPG SD ratio between responders and non-responders did not reach significance ( $P=0.06$ ) but was the only PPG parameter with significance in logistic regression analysis. Neither P-SD2 nor the SD ratio significantly improved the prediction of the response to tracheal intubation in the ROC analysis.

Vasoconstriction not only lowers the PPG amplitude but also moves the dicrotic notch of the pulse wave proximally towards the systolic peak.<sup>17,18</sup> This was measured by the relative notch position (relative distance of the notch from the baseline of the pulse wave on the y-axis). The change of the relative notch position induced by tetanic stimulation was also similar in the groups and in responders and non-responders to tracheal intubation. Seitsonen and colleagues<sup>19</sup> compared EEG, PPG and HR response induced by skin incision between subjects with and without motor response. The change in EEG response entropy, RR interval and PPG notch amplitude were parameters independently associated with motor response to the same stimulus (skin incision). Conversely our intention was to predict the response to a strong stimulus with the response to a weaker 'test stimulus', which turned out to be illusive.

Various definitions for haemodynamic response to tracheal intubation have been used in previous studies. The definition previously used by Gan and colleagues,<sup>14</sup> with an absolute upper limit of HR instead of a relative increase, better represents the general notion of perioperative tachycardia as risk factor of perioperative cardiac morbidity<sup>20,21</sup> than an absolute or relative HR increase, where the maximal HR after stimulation may still be normal.

The effect site remifentanil concentration was computed from the recorded dosing history using the pharmacokinetic and pharmacodynamic parameter set of Minto and colleagues.<sup>11</sup> As stimulation and tracheal intubation were performed [mean (SD)] 11 (2.4) and 14 (2.5) min after induction of anaesthesia, respectively, the remifentanil concentrations were at steady state. Similar remifentanil concentrations could have been achieved with a target-

controlled infusion system, although this would not have changed the concentration range and thus the overall results.

We can only speculate on why the parameters measuring the response to the experimental pain stimulus did not better reflect the anaesthetic level than the parameters computed before stimulation and why they were so poorly predictive. First, the type and intensity of the stimulus may not be adequate and perhaps the response to another pain stimulus, which would provide a better experimental pain model for the surgical stimulation, would better reflect the opioid level. Second, the selected response variables may not be adequate or may have been affected by other unknown variables. Third, the inter-individual variability of the PPG response to stimulation may be greater than the drug-induced effect on this parameter. The infusion, which was on the same arm as the pulse oximeter probe, theoretically could have influenced the skin temperature, the local perfusion and thus the plethysmography signal. The amount of fluid administered until tracheal intubation was low and the individual data were normalized to the value before stimulation.

We conclude that PPG variation induced by a 5 s, 60 mA electrical tetanic stimulus does not reflect haemodynamic responsiveness and hence the analgesic state in a wide clinical range of anaesthesia. The analgesic drug concentration and the hypnotic depth remain the only predictors of haemodynamic responsiveness and analgesia in the anaesthetized patient.

## Acknowledgement

This study was funded solely by the research fund of the Department of Anaesthesiology, University Hospital of Bern, Switzerland.

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